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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,085	05/03/2006	Shinji Okano	50026/058001	5137

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
11/05/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/578,085	OKANO ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/21/09*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-7,10,11 and 13-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-7,10,11 and 13-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/21/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/21/09 has been entered.

Amended claims 2-7, 10-11, 13-24 and new claims 25-29 are pending in the present application.

Response to Amendment

The rejection under 35 U.S.C. 102(a) as being anticipated by Shibata et al. (The 10th Annual Meeting 2004, August 05-06, Poster 088; IDS) was withdrawn in light of Applicant's submission of *a* translation of foreign priority papers.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for suppressing tumor growth comprising the step of delivering **an autologous or allogeneic Sendari virus vector-containing mature dendritic cell to a tumor site, wherein the mature dendritic cell was pulsed or primed with a tumor antigen**;

does not reasonably provide enablement for a method for suppressing tumor growth as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. ***This is a new ground of rejection.***

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The instant specification is not enabled for a method for suppressing tumor growth as broadly claimed for the reasons discussed below.

1. The breadth of the claims

The instant claims are directed to a method for suppressing tumor growth comprising the step of delivering a Sendari virus vector-containing mature dendritic cell derived from any source (e.g., autologous, allogeneic and xenogeneic cells) to a tumor site (*in vivo*) by any route of administration at any site not necessarily limited in an area

surrounding the tumor, and that the mature dendritic cell may not even be pulsed or primed with any tumor antigen and/or the Sendai virus vector may or may not contain a foreign gene (e.g., including one that may or may not encode for a cytokine or a tumor antigen peptide).

2. The state and the unpredictability of the art

At the effective filing date of the present application (11/04/2003), little was known in the prior art for a method of suppressing tumor growth in vivo or at a tumor site simply administering mature dendritic cells comprising a Sendai virus that does not even contain any therapeutic gene (e.g., one that encodes a cytokine or a tumor antigen peptide) or the mature dendritic cells are not even be pulsed or primed with any tumor antigen or the dendritic cells are derived from any source, including xenogeneic dendritic cells, as encompassed by the instant claims as evidenced by at least the teachings of Song et al. (US 2002/0123479 A1), Steinman et al (US 6,300,090; Cited previously), Rice et al (US 2006/0002899) and Gilboa et al (US 2006/0121003).

3. The amount of direction or guidance presented

The instant specification fails to provide sufficient guidance for a skilled artisan on how to suppress tumor growth in a method as broadly claimed. There is no evidence of record indicating that a tumor suppression has been successfully attained in vivo by simple administration of mature dendritic cells comprising a Sendai virus that does not contain any therapeutic heterologous gene (e.g., one that encodes a cytokine or a tumor antigen) at any site or the use of the mature dendritic cells that have not been pulsed or primed with any tumor antigen in any form. Nor is there any evidence of

record indicating that mature xenogeneic dendritic cells can be sustained and withstand a vigorous host immune response for a sufficient period of time to activate specific host immune responses targeted specific to a tumor in need of treatment. Since the prior art at the effective filing date of the present application did not provide such guidance, it is incumbent upon the present application to do so.

As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues discussed above, the state of the relevant art, and the breadth of the instant claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

New claims 28-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. ***This is a new ground of rejection.***

In both new claims 28-29, it is unclear what is encompassed by the term "the cell". Does the term refer to the cell that is contacted with Sendai virus vector? This is because in claims 2 and 25-27, there are different cells such as an immature dendritic cell, a precursor of a dendritic cell or a CD11c+. Clarification is requested because the metes and bounds of the claims are not clearly determined. For the purpose of a compact prosecution, the examiner interprets the term "the cell" in these claims to be meant a CD11c+ cell that is contacted with a Sendai virus vector.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 21 is rejected under 35 U.S.C. 102(b) as being anticipated by Jin et al. (Gene therapy 10:272-277, February 2003; IDS) as evidenced by Romani et al. (J. Exp. Med. 180:83-93, 1994; Cited previously). ***This is a new ground of rejection.***

The claim is directed to an isolated precursor of an immature dendritic cell comprising a Sendai virus vector.

Jin et al already disclosed a method in which recombinant Sendai virus is in contact and provides a highly efficient gene transfer into human cord blood CD34+ cells, including human cord blood HSCs and more immature cord blood progenitor cells (see at least the abstract; page 276, col. 1, last paragraph). Human cord blood CD34+ cells are precursors of dendritic cells (both mature or immature dendritic cells) as evidenced at least by the teachings of Romaini et al which disclose that CD34+ cord blood cells could give rise to dendritic cells under an appropriate culture conditions, as well as by the definition of the term "precursor cells" by the instant specification to be cells (e.g., CD34+ cells) that can differentiate into dendritic cells in the presence of appropriate cytokines (page 16, lines 13-23).

Therefore, the teachings of Jin et al meet all the limitation of the claim as broadly written. Therefore, the reference anticipates the instant claim.

Claims 2-3, 10-11, 19, 21 and 23-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Gary-Gouy et al (J. Interferon and Cytokine Res. 22:653-659, 2002; IDS). ***This is a new ground of rejection.***

Gary-Gouy et al already described at least the isolation of plasmacytoid dendritic cells (CD123+CD11c-) and CD11c+ myeloid dendritic cells form human blood donors, and incubated each of the isolated cell population in the absence or presence of cytokines prior to infection with Sendai virus which is a vector (see at least the sections titled "Cell purification" and "Type 1 IFN assay" on page 654 and the section titled "Monocytes and CD123hi PDC but not CD11c+ MDC produce IFN-1 on specific

stimulation" on page 655). The plasmacytoid cells are known to be predendritic cells (PDC) or DC precursor cells (page 653, col. 1 continues to first paragraph of col. 2). Additionally, since CD11c+ myeloid dendritic cells taught by Gary-Gouy do not express markers such as CD80, CD83 and CD86 nor were they subjected to further stimulation by LPS; they fall within the scope of "immature dendritic cells" as defined by the present application (see at least page 10, lines 16-20; page 11, lines 14-19).

Accordingly, the various isolated CD123+CD11c-) and CD11c+ myeloid dendritic cell populations treated in the presence or absence of cytokines prior to the infection with Sendai virus taught by Gary-Gouy et al are indistinguishable from the isolated cells comprising a Sendai virus vector as broadly claimed. Additionally, it should be noted that the spontaneous maturation of immature dendritic cells to matured dendritic cells is the inherent property of a Sendai virus vector; and therefore the method taught by Gary-Goury is also indistinguishable from the method as broadly claimed because it contains the same method step and the same starting materials.

Furthermore, please, also note that where, as here, the claimed and prior art products are identical **or** substantially identical, **or** are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke. Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton,

and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Therefore, the reference anticipates the instant claims.

Claims 11, 16-19 and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Pickles et al (US 2005/0048030; IDS).

The examiner interprets claims 11, 16-19 to be **product-by-process claims**.

Pickles et al teach at least a method for transferring a nucleotide sequence to a cell *in vitro* or *ex vivo* using a recombinant paramyxovirus vector, wherein the cell can be a human dendritic cell (see at least paragraphs 122-130), the recombinant paramyxovirus vector includes Sendai virus vector (at least paragraphs 43-45) and the nucleotide sequence encodes a cytokine such as beta-interferon or a tumor antigen (paragraphs 86, 92-103). It should be noted that the transfected dendritic cells that are taught by Pickles et al are inherently mature dendritic cells regardless whether the dendritic cells are mature and/or immature prior to transfection because of the spontaneous maturation of immature dendritic cells to matured dendritic cells by a Sendai virus vector; and therefore they are indistinguishable from the isolated mature dendritic cell as claimed.

Once again, please, also note that where, as here, the claimed and prior art products are identical **or** substantially identical, **or** are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his

claimed product. See In re Ludtke. Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Therefore, the reference anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2-7, 10-11, 13-14 and 13-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Song et al. (US 2002/0123479 A1) in view of Tokusumi et al. (US 6,746,860; IDS), Jin et al. (Gene therapy 10:272-277, February 2003; IDS), Hwu et al (US 6,734,014) and Waller et al (US 2005/0013810). ***This is a modified rejection.***

Within the scope of enablement, Song et al disclose compositions and methods useful for stimulating an immune response against one or more disease associated antigens, including cancer associated antigens, by genetically modifying dendritic cells including dendritic progenitor cells as well as dendritic cells having CD11c+ maker, *in vivo* or *ex vivo*, wherein the dendritic cells were genetically modified by a recombinant negative strand RNA virus (e.g., vesicular stomatitis virus, paramyxoviruses, orthomyxoviruse and bunyaviruses) directing the expression of at least one disease associated antigen (see at least Summary of the Invention; particularly paragraphs 6-7, 9-12, 16-18, 41-45, 60 and Figure 1). Since the starting dendritic cells (including both dendritic cells and dendritic progenitors) used by Song et al do not express markers such as CD80, CD83 and CD86 (see at least Figure 1 for cellular dendritic cell markers taught by Song et al; paragraphs 9, 41-44), they fall within the scope of "immature dendritic cells" as defined by the present application (see at least page 10, lines 16-20; page 11, lines 14-19). With respect to new claims 25-29, it is further noted that the transfected dendritic cells were not further subjected to any additionally treatment such as LPS stimulation for high expression of matured dendritic cell markers of CD80, CD83 and CD86. Song et al also disclose that it has been discovered that the efficiency of immune system stimulation mediated by genetically modifying dendritic cells can be

several orders of magnitude greater than that mediated by genetically modified fibroblasts, muscle, and other cell types (paragraph 39). Song et al further disclose that an expression vector may in addition to directing expression of at least one disease associated antigen, directs the expression of an immunomodulatory factor such as IL-12, IL15, IL-2, beta-interferon among many others (paragraphs 68, 89-90). Song et al also teach that the genetically modifying dendritic cells, including allogeneic cells, are typically administered via parenteral or other traditional direct routes or directly into a specific tissue such as into the tumor in the case of cancer therapy in a mammal (e.g., a human) in need thereof (paragraphs 16-18, 43, 140, 164 and 176).

Song et al did not teach explicitly the use of a Sendai virus vector for genetically modifying immature dendritic cells, including dendritic progenitor cells, even though they disclosed that dendritic cells, including dendritic progenitor cells could be genetically modified by any recombinant negative strand RNA virus including any paramyxovirus; nor did Song et al teach specifically the use of CD34+ dendritic precursor cells or the step of further culturing the CD34+ precursor cells with GM-CSF and IL-4.

However, at the effective filing date of the present application, Tokusumi et al already disclosed the preparation of at least a recombinant Sendai virus vector to be used for transfer of foreign genes (see at least the abstract as well as Summary of the Invention). Tokusumi et al further disclosed that the Sendai virus vector is useful for gene therapy due to its safety, high gene transfer efficiency and capacity to express a foreign gene in a high level.

Additionally, Jin et al already disclosed successfully a method in which recombinant Sendai virus was in contact and provided **a highly efficient gene transfer into human cord blood CD34+ cells**, including human cord blood HSCs and more immature cord blood progenitor cells (see at least the abstract; page 276, col. 1, last paragraph).

Moreover, Hwu et al also taught at least a method of preparing recombinant dendritic cells by transforming a hematopoietic stem cell, including CD34+ cells derived from a variety of sources such as cord blood, bone marrow and mobilized peripheral blood, with a nucleic acid followed by differentiation of the stem cell into dendritic cells in the presence of GM-CSF, TNF-alpha and optionally together with IL-4 (see at least the abstract; col. 9, lines 29-57; col. 10, line 60 continues to line 13 of col. 11; col. 15, lines 15-46).

Furthermore, Waller et al also taught that progenitors of dendritic cells can be identified in many tissues, such as bone marrow and blood, based on the expression of certain cell surface markers; and that dendritic cell progenitors are typically identified by the expression of one or more of the following markers on its cell surface **CD11c**, CD13, CD14, CD33, **CD34** or CD4 (see at least paragraphs 24-28 and 36).

Accordingly, it would have been obvious and within the scope of skill for an ordinary skilled artisan to modify the teachings of Song et al. by also utilizing a recombinant Sendai virus vector for genetically modifying immature dendritic cells, including CD11c+ and/or CD34+ dendritic precursor cells derived from bone marrow or cord blood to produce mature dendritic cells expressing at least a recombinant disease

associated antigen as encompassed by the instant claims in light of the teachings of Tokusumi et al., Jin et al, Hwu et al and Waller et al as discussed above.

An ordinary skilled artisan would have been motivated to carry out the above modifications because Tokusumi et al already taught that the recombinant Sendai virus vector is useful for gene therapy due to its safety, high gene transfer efficiency and capacity to express a foreign gene in a high level. Additionally, a highly efficient gene transfer in human cord blood CD34+ cells which are dendritic precursor cells has been successfully achieved and demonstrated by Jin et al. Furthermore, dendritic cell progenitors typically identified at least by the expression of one or more of the following markers on its cell surface such as **CD11c** or **CD34**, derived from a variety of sources such as cord blood, bone marrow and mobilized peripheral blood, have been genetically modified for the preparation of mature dendritic cells expressing desired heterologous proteins/peptides as taught by Hwu et al and Waller et al.

The methods and compositions resulted from the combined teachings of Song et al., Tokusumi et al., Jin et al., Hwu et al and Waller et al are indistinguishable from the methods and compositions as claimed by the present application.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Song et al., Tokusumi et al., Jin et al., Hwu et al and Waller et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above modified rejection in the Amendment filed on 9/21/09 (pages 7-18) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

1. Once again, Applicants argue that there was no reasonable expectation that Sendai virus could successfully be used to produce a mature dendritic cell using an immature dendritic cell or a precursor thereof. This is because the primary Song et al reference demonstrated only transduction of dendritic cells with a retrovirus vector and the transduction efficiency of dendritic cells was extremely low. Applicants referred again to the teachings of Cremer et al (Hum. Gene Ther. 11:169-1703, 2000; IDS) showing that one could probably obtain IFN-beta-transformed DCs only by transducing CD34+ stem cells (progenitors of dendritic cells) with a recombinant retroviral vector. Applicants further argued that transducing dendritic cells using viral vectors is not trivial and Applicants demonstrated that immature dendritic cells are very efficiently infected with Sendai virus vector, with the gene transfer efficiency to CD34+ precursor cells at 65 to 70% versus the result reported by Cremer et al (<25 or 30%). Applicants further noted that infectivity of Sendai virus to matured dendritic cells was significantly reduced and a highly efficient gene transduction specific to immature dendritic cells using Sendai virus vector was an unpredictable finding of the present invention. Additionally, Song would not suggest to one skilled in the art to use a Sendai virus vector because Song expressly indicates that a recombinant retroviral vector is a "preferred embodiment" (paragraph 52). With respect to the Cremer reference cited by Applicants, Applicants

argue that the reference is relevant to the state of the art at the time of filing of the present application.

Firstly, the above rejection is made under 35 U.S.C. 103(a) and therefore there is no requirement that the primary Song et al reference has to teach the use of a Sendai virus vector, let alone demonstrating specifically transfection of a precursor of a dendritic cell (e.g., CD34 cells) with a Sendai virus vector. Nevertheless, Song et al taught specifically compositions and methods useful for stimulating an immune response against one or more disease associated antigens, including cancer associated antigens, by genetically modifying dendritic cells including dendritic progenitor cells, *in vivo* or *ex vivo*, wherein the dendritic cells were genetically modified by a recombinant negative strand RNA virus (e.g., vesicular stomatitis virus, paramyxoviruses, orthomyxoviruse and bunyaviruses) directing the expression of at least one disease associated antigen. At the effective filing date of the present application, the teachings of Song et al are enabled as evidenced at least by the teachings of Jin et al, Li et al, Steinman et al, and Gary-Gouy et al as discussed further below. Furthermore, the teachings of Song et al are not limited only to preferred embodiments; and therefore there is no "teaching-away" whatsoever by the Song reference as argued by Applicants.

Secondly, in contrast to Applicant's position that highly efficient gene transduction to immature dendritic cells or dendritic precursor cells such as CD34 stem cells by Sendai virus vector was unpredictable at the effective filing date of the present application, **the teachings of Jin et al cited in the above rejection indicated otherwise**. Furthermore, Li et al (J. Virol. 74:6564-6569, 2000; IDS) also demonstrated

that **a Sendai virus vector mediated a gene transfer and expression in various types of animal and human cells, including non-dividing cells, with high efficiency** (see at least the abstract).

Thirdly, at the effective filing date of the present application **Steinman et al (US 6,300,090) already successfully transfecting proliferating or non-proliferating human dendritic cells (both mature and non-mature cells) with at least a recombinant influenza viral vector which is minus-strand RNA viral vector that belongs to the same family as Sendai virus vector (see at least issued claims of US 6,300,090)**. Furthermore, **Gary-Gouy et al already demonstrated that plasmacytoid dendritic cells (CD123+CD11c-) and CD11c+ myeloid dendritic cells as well as peripheral blood monocytes from human blood donors were infected readily by a Sendai virus** (see at least the sections titled "Cell purification" and "Type 1 IFN assay" on page 654 and the section titled "Monocytes and CD123hi PDC but not CD11c+ MDC produce IFN-1 on specific stimulation" on page 655).

Fourthly, the instant claims do not require any particular transfection efficiency and the combined teachings Song et al., Tokusumi et al., Jin et al., Hwu et al and Waller et al as set forth in the above rejection meet all the limitation of the claims as written.

Fifthly, it should be noted that the state of the prior art at the filing date of the present application was not defined exclusively by the teachings of the Cramer reference cited by Applicants. Once again, please refer at least to all of the teachings of the cited prior art used in the rejections of record.

2. With respect to the Tokusumi reference, Applicants argue that the reference merely shows a working example using established cell line derived from kidney epithelial cells of macaque monkey; and it does not concern to immature dendritic cells or precursors of dendritic cells. With respect to the Jin reference, Applicants argue that this reference does not teach or suggest the successful differentiation of CD34+ cells containing Sendai virus into mature dendritic cells; and that there was no reasonable expectation that Sendai virus could be transduced into CD34+ cells without disturbing differentiation of the cells into dendritic cells, maturation of dendritic cells or the function of mature dendritic cells. Applicants further noted that CD34+ cell infected with Sendai virus are not a claimed subject matter. With respect to the Hwu reference, Applicants argue that Hwu only provided experimental data using retrovirus vectors and that experiments using retrovirus vector do not provide a reasonable expectation of success of the gene transfer of Sendai virus vector into dendritic cells. With respect to the Waller reference, Applicants argue that the reference merely describes gene markers of dendritic cell progenitors.

Firstly, the examiner notes that Applicants appear to consider each of the cited references in total isolation one from the others; and this is improper. As already pointed above, the above rejection is made under 35 U.S.C. 103(a) and therefore none of the cited references has to teach every elements of the claims.

Secondly, with respect to the issue of unreasonable expectation of success that Sendai virus could be transduced into CD34+ cells without disturbing differentiation of the cells into dendritic cells and/or Sendai virus vector into dendritic cells as argued by

Applicants; please refer at least to the teachings of Steinman et al (US 6,300,090), Gary-Gouy et al (J. Interferon and Cytokine Res. 22:653-659, 2002; IDS) and Hwu et al (US 6,734,014). There was no evidence from any of these teachings that Sendai virus, retrovirus or any other viral vector would adversely affect the differentiation of dendritic precursor cells, including CD34+ precursor cells, into dendritic cells. Furthermore, **Steinman et al already successfully transfecting proliferating or non-proliferating human dendritic cells (both mature and non-mature cells) with at least a recombinant influenza viral vector which is minus-strand RNA viral vector that belongs to the same family as Sendai virus vector; and Gary-Gouy et al already demonstrated that plasmacytoid dendritic cells (CD123+CD11c-) and CD11c+ myeloid dendritic cells as well as peripheral blood monocytes from human blood donors were infected readily by a Sendai virus**/

Thirdly, with respect to the issue that CD34+ cells infected with Sendai virus are not the claimed subject matter; please refer at least to claims 2, 4-5, 20-21 of the present application.

3. Applicants further argue that the art of record provides no basis for a reasonable expectation of success with respect to tranducing an immature dendritic cell or a precursor thereof which, in turn, produces mature dendritic cells. This is because the inventors have demonstrated a surprising and unexpected beneficial effect that Sendai virus transduction into immature dendritic cells induces spontaneous maturation of transduced dendritic cells without any stimulation using LPS. With respect to the

open language of the term "comprising", Applicants argue that even if other stimulation were given to dendritic cells, it can not be concluded that the spontaneous maturation (measured by the suppression of phagocytosis and high level expression of CD80, CD83 and CD86 markers) does not occur. Stimulation in addition to the use of Sendai virus may have an additional beneficial effect but the additional stimulation does not replace the effect seen with Sendai virus alone, and that the term "comprising" does not negate the nonobviousness of the presently claimed invention. Applicants further argue that the basis for rejection is not applicable to new claim 25 which excludes further stimulation for maturation.

Firstly, as already noted in the above rejection the methods and compositions resulted from the combined teachings of Song et al., Tokusumi et al., Jin et al., Hwu et al and Waller et al **are indistinguishable** from the methods and compositions as claimed by the present application. **Moreover, the spontaneous stimulation of immature dendritic cells to mature dendritic cells which are defined as dendritic cells having high expression of CD80, CD83 and CD86 is the "intrinsic property" of a Sendai virus**. Therefore, this intrinsic property of a Sendai virus would occur in the methods and compositions resulted from the combined teachings of Song et al., Tokusumi et al., Jin et al., Hwu et al and Waller et al; regardless whether any of these inventors are aware of. This is also an evidence that **the above 103 rejection was not** based on hindsights and/or reconstructed based on the specification of the present application.

Secondly, with respect to new claims 25-29 it is further noted that the transfected dendritic cells taught by Song et al were not further subjected to any additionally treatment such as LPS stimulation for high expression of matured dendritic cell markers of CD80, CD83 and CD86.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11, 13-19 and 23-24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-6 and 8-14 of copending Application No. 11/630,532. ***This is a new ground of rejection.***

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

The instant claims are directed to an isolated vector-containing mature dendritic cell containing a Sendai virus vector; an isolated immature or mature dendritic cell comprising a Sendai virus vector; and a method for suppressing tumor growth comprising the step of delivering the same mature dendritic cell to a tumor site.

Claims 1, 3-6 and 8-14 of copending Application No. 11/630,532 are drawn to an anticancer agent comprising a dendritic cell introduced with an RNA virus able to replicate its genome, including the RNA virus encodes an IFN-beta; and a method for suppressing a cancer comprising the step of administering a dendritic cell introduced with an RNA virus able to replicate its genome.

The claims of the present application differ from the claims of the copending Application No. 11/630,532 in reciting specifically Sendai virus vector and mature/immature dendritic cells.

The claims of the present application can not be considered to be patentably distinct over claims 1, 3-6 and 8-14 of copending Application No. 11/630,532 when there are specific disclosed embodiments of the copending Application that teach that the preferred RNA viruses of the invention include paramyxoviridae virus such as Sendai virus (page 5, lines 1-36; and examples); and dendritic cells include both mature and immature dendritic cells (page 8, lines 3-4). Accordingly, the claims of copending Application No. 11/630,532 fall within the scope of claims 11, 13-19 and 24 of the present application.

This is because it would have been obvious to an ordinary skilled artisan to modify the claims of the copending Application by introducing a minus-strand RNA viral vector such as Sendai viral vector into dendritic cells (both mature and/or immature dendritic cells) for the preparation of an anticancer agent, that support the instant claims. An ordinary skilled artisan would have been motivated to do this because these embodiments are explicitly disclosed or taught in the copending Application No. 11/630,532 as preferred embodiments.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicants' argument related to the above rejection in the Amendment filed on 9/21/09 (pages 18-19) has been fully considered but it is respectfully not found persuasive.

Applicants argue basically that the provisional rejection should be withdrawn since the present application is an earlier filed application with respect to the copending Application No. 11/630,532 and that if the provisional obviousness-type double patenting rejection is the last remaining rejection in the present case.

It is noted that the provisional obviousness-type double patenting rejection **is not** the last remaining rejection in the present case.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Siegal et al (Science 284:1835-1837, 1999) teach explicitly that type 2 dendritic cells can be differentiated from DC2 precursor (pDC2) cells by culturing them with IL-3 or IL3 +CD40 ligand for 6 days.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

/QUANG NGUYEN/
Primary Examiner, Art Unit 1633